REMARKS

I. Amendments to the claims

Upon the entry of the amendment, claims 1-10, and 15-22, will be pending. Claims 1-4, 7, 10, 15-17, and 19 have been amended to claim the subject matter of the invention with greater particularity and specificity. New claim 22 has been added. Claims 11-14 were previously cancelled. Claims 18, 20 and 21 are withdrawn.

The specification has been also amended to provide a generic meaning to the trade name Trasylol®. Amendments to claims and specification merely clarify the language of claims and specification. No new matter has been introduced by the amendments.

Claim 1 now recites "human Kunitz-type serine protease inhibitor." The limitation "human" is disclosed throughout the original specification. See, e.g., page 10, line 33.

Newly added claim 22 now includes the limitation

> "wherein the rate of mucociliary clearance is increased by more than about 30 per cent, compared with the rate of mucociliary clearance in the absence of the treatment."

This limitation is supported by the specification, for instance, by Example 21 (page 80, line 35 through page 81, line 4), as further illustrated by FIG. 22. As can be seen from the chart on FIG. 22, 8 hours after administering 3 ml of 3 mg/mL aerosol of the inhibitor bikunin, the tracheal mucus velocity (TMV) for a sheep was at about 98 % of the baseline, while for the vehicle only, the TMV was about 76 %. Accordingly, using the inhibitor increased the TMV by about 30%. In Example 25, as illustrated by FIG. 26, a substantial increase in the value of the TMV was also observed. As shown by FIG. 26, 2.5 hours after administering the inhibitor, the increase in the value of the TMV was more than 30 %, i.e., from about 3 mm/min average for

compositions with HBSS only (no inhibitor), to about 9 mm/min average, the increase being about 200% over HBSS treatment.

Additionally, the Office Action requested the Applicants to re-submit a copy of the sequence listing in a computer readable form (CRF) (paragraph [9] on page 3 of the Office Action). A computer disk having the sequence, and a declaration stating compliance with 37 C.F.R. § 1.821 (f) are attached herewith.

The Substituted Sequence Listing submitted herewith is identical to the previously filed Listing with the exception of the new docket number.

II. Objections to the Specification

In paragraph [10] on page 4 of the Office Action the Office Action objected to the use of trademark Trasylol® because it is not capitalized throughout the specification. The Applicants respectfully point out that using of the trademark symbol ® following the word is a permissible alternative to capitalization (see, MPEP § 608.01(v), right-hand column on page 600-88 of the MPEP). The Applicants added a generic description of the trade name. Accordingly, the withdrawal of the objection is respectfully requested.

III. Rejection Under 35 USC § 112, First and Second Paragraphs and Double Patenting Rejection

The Applicants have noted and acknowledged the fact that the Examiner has withdrawn the previous rejections under 35 USC § 112, first and second Paragraphs (paragraphs [11]-[13] on pages 4-5 of the Office Action). The Applicants have also noted and acknowledged the fact that the Examiner has withdrawn the previous double patenting rejection (paragraph [16], page 6 of the Office Action).

IV. Rejection Under 35 U.S.C. § 103(a)

Claims 1-10, 15-17, and 19 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the patent document WO 97/33996 to Tamburini et al. (hereinafter, "Tamburini") in view of the article by Rasche et al. (hereinafter, "Rasche") and the article by O'Riordan et al. (hereinafter, "O'Riordan"). This rejection is respectfully traversed on the following grounds.

To establish a *prima facie* case of obviousness, the following three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference(s) as proposed by the Examiner; (2) there must be a reasonable expectation of success and (3) the prior art reference(s) must teach or suggest all of the claim limitations. The Applicant respectfully submits that none of the criteria have been satisfied in this case because Tamburini does not disclose nor suggest every limitation of claims 1-10, 15-17, and 19, and the combination of Rasche and O'Riordan fails to cure this deficiency.

Briefly, the claimed invention contains Examples 11-26 which is not disclosed in Tamburini. Examples 11-16 are the subject matter of co-pending application U.S. Serial No. 09/218,913; and Examples 17-26 are the subject matter of the instant invention. Together, Examples 11-26 disclose human placental bikunin sequences and fragments thereof for use in increasing mucociliary clearance (MCC) by the measurement of tracheal mucus velocity (TMV) *in vivo*, decrease or inhibition of the potential difference across the tracheal epithelium *in vivo,* and decrease or inhibition of the sodium current in various cultured cell lines (e.g. HBE, OVE, CHO and human cystic fibrosis HBE cells) *in vitro*.

Tamburini does not disclose any working examples relating to that disclosed by Examples 17-26 of the instant application. Although Tamburini discloses the identical human placental bikunin sequence and fragments thereof, Tamburini discloses that these sequences are

effective in inhibiting various protease inhibitors as shown in Tables 3-9 and Examples 1-10, and not their use to increase MCC. Additionally, Tamburini discloses that human placental bikunin is much more effective than bovine derived aprotinin as a serine protease inhibitor (see Tables 3-9 comparing various human placental bikunin sequences to that of aprotinin/Trysalol®). Hence, because there are no working examples nor suggestions in Tamburini that the human placental bikunin sequences disclosed are effective to increase the rate of MCC, or inhibit the potential difference and the sodium current thereby increasing MCC, Tamburini alone does not make the claimed invention obvious.

Moreover, in the Office Action mailed October 3, 2003 (paper no. 19) and mentioned in this Office Action, recognized that, "Tamburini et al. do not teach administration of their human placental bikunin and fragments thereof increase the rate of mucociliary clearance in a subject (see, page 13, lines 5-6)." Therefore, in order to be a proper prior art reference, Tamburini must disclose the method treatment of a patient using a human Kunitz-type serine protease inhibitor (i.e. human placental bikunin) having at least one sequence specified in claim 1. As a result of such treatment, the rate of mucociliary clearance must increase. None of these limitations is disclosed by Tamburini. As discussed above, all that is described by Tamburini is the use of such sequences to inhibit various protease inhibitors (see Tables 3-9 and Examples 1-10).

Hence, there must be some suggestion or motivation to modify Tamburini and that the combination of the cited references gives a reasonable expectation of success, and teach or suggest all of the claim limitations. In the absence of the above, a *prima facie* case of obviousness is not met. A *prima facie* case of obviousness is not met because there is first no suggestion in Tamburini to use aprotinin/Trysalol®. Tamburini discloses that human Kunitz-type serine proteases have improved inhibitory function. So, Rasche by using aprotinin/Trysalol® to treat patients with chronic obstructive bronchitis to increase the rate of expectoration of mucus cannot be used in combination with Tamburini because Tamburini actually *teaches away* from using aprotinin/ Trysalol®.

In addition, all that is disclosed by Rasche et al. is achieving less airway resistance ("impressive airway resistance drop") as well as making the "initially very viscous sputum" liquid-like (Section 4, fourth full paragraph of the English translation). There is nothing disclosed with regard to the rate of mucociliary clearance. To conclude that the rate of mucociliary clearance will increase just because the airway resistance and the viscosity of the sputum dropped would be speculative. It is possible to have a situation when the airway resistance has dropped and the sputum has liquefied and yet the mucociliary clearance has not improved for reasons other that the airways resistance or the viscosity of the sputum. Thus, combining Rasche with Tamburini is not suggested, and the combination does not teach all the claim limitations.

Turning now to the O'Riordan, O'Riordan states that mucociliary clearance is "partly dependent on increased elastase activity, and that elastase inhibitors may be useful in protecting against mucociliary dysfunction (abstract)." However, O'Riordan does not suggest which proteins or neutrophil elastase inhibitors are suitable. So the rational for combining Rasche and O'Riordan is that aprotinin/Trysalol® is known to inhibit neutrophil elastase because that was disclosed in Tamburini (see Table 3 of Tamburini). Yet, although Tamburini discloses both human placenta bikunin and aprotinin/Trysalol® inhibit neutrophil elastase, Tamburini actually *teaches away* the use of aprotinin/Trysalol® because the human placenta bikunin sequences and fragments thereof have improved inhibitory functions over aprotinin/ Trysalol®, e.g. at least 2.5 times more potent than aprotinin (see Table 3 wherein bikunin inhibited neutrophil elastase with a Ki of 323 nM, whereas the Ki value of aprotinin/ Trysalol® is 8.5 μM or 8500 nM).

Therefore, the combination of the disclosures of Rasche and O'Riordan fails to cure the deficiencies of Tamburini, and the combination of Tamburini, Rasche and O'Riordan are not suggested in Tamburini, and the combination of references do not describe all the claim limitations (see claim 1).

Accordingly, in view of the foregoing, withdrawal of the rejection of claims 1-10, 15-17, and 19 under U.S.C. § 103(a) is respectfully requested.

V. CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

If any additional fee is required, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07 -1896.

Respectfully submitted,

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Lisa A. Haile, J.D., Ph.D.
Registration No.: 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO CUSTOMER NUMBER 28213